HOSPITAL CHRONICLES 2012, VOLUME 7, SUPPLEMENT 1: 44–53

ANTITHROMBOTIC THERAPY IN CARDIOLOGY

New Anti-Thrombotic Drugs in Acute Coronary Syndromes and Percutaneous Coronary Intervention. The Role of Prasugrel, Ticagrelor and Cangrelor

Constantinos Stratos, MD, FESC, Alexandros Kouloubinis, MD

1st Cardiology Department, MITERA Hospital, HYGEIA Group, Athens, Greece

KEY WORDS: *antithrombotic therapy; antiplatelet agents; aspirin; clopidogrel; prasugrel; ticagrelor; cangrelor; acute coronary syndrome; percutaneous coronary intervention; coronary stents*

ABBREVIATIONS
ACS = acute coronary syndrome(s)
ADP = adenosine diphosphate
ATP = adenosine triphosphate
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CI = confidence intervals
COX = cyclooxygenase
CrCl = creatinine clearance
CYP = cytochrome P
DAPT = dual anti-platelet therapy
HR = hazard ratio
MI = myocardial infarction
NNT = number needed to treat
NSTE = non-ST elevation
NSTEMI = non-ST elevation myocardial infarction
RR = relative risk
STEMI = ST elevation myocardial infarction
TIMI = thrombolysis in myocardial infarction

Correspondence to:
Constantinos Stratos, MD, FESC
Head of 1st Cardiology Department
MITERA Hospital, HYGEIA Group
Athens
6 Erythrou Stavrou St.,
Maroussi 151 23, Attiki, Greece
Tel.: +30 2106869675/+30 2106869675
E-mail: cstratos@otenet.gr

Conflict of Interest: none declared

ABSTRACT

Antiplatelet drugs constitute the cornerstone therapy in acute coronary syndromes (ACS) and patients undergoing percutaneous coronary intervention (PCI). Aspirin is part of the standard treatment given to these patients, further supplemented by clopidogrel, which both significantly reduce the short- and long-term risk of death and ischemic complications in high-risk settings. However, the pharmacokinetic and pharmacodynamic effects of clopidogrel are highly variable and may be influenced by genetic polymorphisms, which lead to reduced therapeutic responses and clopidogrel "nonresponders". Two newer oral adenosine diphosphate blockers, prasugrel and ticagrelor, have already entered clinical practice, associated with less interpatient variability and a more potent antiplatelet effect. In recent studies, both prasugrel and ticagrelor were shown to be superior to clopidogrel in patients with ACS who were undergoing PCI; based on the results of these studies, cardiological societies have recently updated their guidelines and have included these agents into their recommendations. In this review, these newer oral antiplatelet agents, their effects and clinical results are discussed, together with the preliminary results of another new intravenous antiplatelet agent, cangrelor, which can bridge the discontinuation of the oral agents up to the time of surgery when needed.

INTRODUCTION

Platelet activation and subsequent aggregation play a dominant role in the propagation of arterial thrombosis and consequently are the key therapeutic targets in the management of acute coronary syndrome (ACS). Platelets can be activated through many pathways. Inhibition of such a pathway results only in partial attenuation of platelet function. Aspirin irreversibly blocks platelet cyclooxygenase (COX-1), inhibits thromboxane A2 formation and induces a permanent functional inhibition in platelets. As a consequence, aspirin use has been shown to safely reduce ischemic events throughout the spectrum of clinical manifestations of coronary artery disease (CAD). Therefore, aspirin is part of the standard treatment given to patients with CAD, including those undergoing percutaneous coronary intervention (PCI).[1,2]

Despite the inhibition of cyclooxygenase by aspirin, platelet activation can still occur through thromboxane-independent pathways, leading to aggregation of platelets and formation of thrombin. Thus, inhibition of an additional pathway of platelet activation could further reduce platelet activity. As a consequence, the antagonists of P2Y12 receptor have emerged as a major therapeutic tool in ACS.[1,2] Clopidogrel, an oral P2Y12 receptor inhibitor, added to standard regimen with aspirin further reduces the short- and long-term risk of death and ischemic complications in high-risk settings, such as patients with an ACS and those undergoing PCI.[1,3-8] However, the pharmacokinetic and pharmacodynamic effects of clopidogrel are highly variable and may be influenced by genetic polymorphisms, which translate into differential pharmacodynamics and therapeutic responses,[2,9-15] leading to the notion of clopidogrel "nonresponders".[16] Two newer oral adenosine diphosphate (ADP) blockers, prasugrel and ticagrelor, have been associated with less interpatient variability and a more potent platelet-aggregation response.[13-15,17] Prasugrel was superior to clopidogrel in patients with ACS who were undergoing PCI,[18-21] and ticagrelor was superior to clopidogrel in patients with ACS.[22-25]

Thus, dual antiplatelet therapy (DAPT) with aspirin and an oral P2Y12 receptor inhibitor is the standard of care to prevent the short- and long-term risk of recurrent atherothrombotic events in high-risk settings, such as patients with an ACS and those undergoing PCI.[1,26-29] However, the ischemic benefit associated with more intense platelet inhibition in these high-risk settings occurs at the expense of an increased risk of bleeding complications.[26-29] Given that the risk of bleeding is significantly increased among patients undergoing surgical procedures, discontinuation of antiplatelet therapy for a time frame that allows recovery of platelet function is warranted. However, premature discontinuation of antiplatelet therapy in these settings has been associated with an increase in ischemic complications[30-33] and substantial morbidity and mortality.[34-37] These findings underscore the need to define strategies of platelet inhibition that allow to safely "bridge" patients to their surgical procedure with minimum risk of ischemic events or bleeding complications. Cangrelor, a nonthienopyridine intravenous (IV) antagonist of the P2Y12 receptor, is characterized by rapid, potent, predictable, and reversible platelet inhibition with rapid offset of effect.[1,13,38] Therefore, this compound has desirable pharmacodynamic properties to be considered for bridging patients to surgery in whom discontinuation of antiplatelet therapy, particularly a P2Y12 receptor inhibitor, can lead to adverse consequences (e.g., stent thrombosis) while preserving normal hemostasis at the time of surgery.[39] According to the BRIDGE study, cangrelor could represent a safe and effective drug for bridging patients treated with irreversible platelet P2Y12 inhibitors such as clopidogrel to coronary artery bypass grafting (CABG) surgery.[40]

PRASUGREL

Prasugrel is a newer thienopyridine, binding irreversibly to platelet P2Y12 receptors. Like ticlopidine and clopidogrel, prasugrel is a prodrug that is inactive in vitro.[41] Prasugrel requires two metabolic steps for formation of its active metabolite, which is chemically similar to the active metabolite of clopidogrel.[14] The first metabolic step requires only plasma esterases; the second step, in the liver, is mediated by CYP enzymes. Finally, more than 80% of the dose received by mouth is converted to the active metabolite. In contrast, clopidogrel is extensively hydrolysed by esterases to inactive metabolites (by 85% – 90%), and the residual prodrug requires two metabolic steps in the liver for formation of its active metabolite. Eventually, only ~2% of a single dose received by mouth is detected on the platelet P2Y12 receptors. As a consequence, while equimolar concentrations of the active metabolites of clopidogrel and prasugrel result in similar levels of platelet inhibition in vitro, the markedly different amounts of each metabolite generated in vivo following a loading dose of clopidogrel (300 mg) or prasugrel (60 mg) result in ~10-fold higher platelet exposure to the latter when compared with the former.[41] This observation provides a pharmacokinetic basis for the faster, more profound and less variable inhibition of platelet function observed with prasugrel when compared with clopidogrel in healthy subjects[41] as well as in patients with ischemic heart disease.[18-21,42,43] Moreover, in contrast to clopidogrel, the lack of drug interaction potential and the apparent independence of CYP2C19 genetic variance and of reduced ABCB1 function result in a predictable and consistent antiplatelet response to prasugrel.[42-44]

Prasugrel was compared with clopidogrel in the TRITON-TIMI 38 trial.[18] The study included 13,608 clopidogrel-naove patients with moderate-to-high-risk ACS undergoing PCI. Cases treated conservatively were not included in this study. Patients were randomly assigned to receive, in addition to aspirin, prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) for 6 to 15 months. The primary efficacy end-point was death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke. The key safety end-point was major bleeding. In the whole cohort, prasugrel therapy for 6 to 15 months was associated with a significantly lower rate of the primary efficacy end-point (9.9% for prasugrel vs. 12.1% for clopidogrel; HR 0.81; 95% CI: 0.73 – 0.90; P <0.001), mostly driven by a significant risk reduction for MI (7.4% vs. 9.7%; HR 0.76; 95% CI: 0.67 – 0.85; P <0.001). It is noteworthy that this beneficial effect of prasugrel appeared very early by the first prespecified time point, at 3 days (4.7 vs. 5.6%; HR 0.82; 95% CI: 0.71 – 0.96; P = 0.01), and persisted throughout the follow-up period. Moreover, from 3 days to the end of the study, there was a progressive

benefit increase in favor of prasugrel (5.6% vs. 6.9%; HR 0.80; 95% CI: 0.70 – 0.93; P = 0.003). Also lower in the prasugrel group was the rate of definite or probable stent thrombosis (1.1% vs. 2.4%; HR 0.48; 95% CI: 0.36 – 0.64; P <0.001), as well as the rate of urgent target-vessel revascularization (2.5% vs. 3.7%; P < 0.001). There was no difference in the rates of either non-fatal stroke or cardiovascular death. With regards to the safety end-point, there was a significant increase in the rate of non-CABG-related TIMI major bleeding among patients receiving prasugrel (2.4% vs. 1.8%;HR 1.32; 95% CI: 1.03 – 1.68; P = 0.03), mostly driven by a significant increase in spontaneous bleeds (1.6% vs. 1.1%; HR 1.51; 95% CI: 1.09 – 2.08; P = 0.01), but not by bleeding related to arterial access (0.7% vs. 0.6%; HR 1.18; 95% CI: 0.77 – 1.82; P = 0.45), which means that long-term exposure to a potent antiplatelet agent is the determinant of bleeding. Life-threatening bleeding was also significantly increased under prasugrel (1.4% vs. 0.9%; HR 1.52; 95% CI: 1.08 – 2.13; P = 0.01), as well as fatal bleeding with prasugrel compared with clopidogrel (0.4% vs. 0.1%; HR 4.19; 95% CI: 1.58 – 11.11; P = 0.002). Significantly more frequent was also bleeding in total (HR 1.31; 95% CI: 1.11 – 1.56; P = 0.002), bleeding requiring transfusion (HR 1.34; 95% CI: 1.11 – 1.63; P <0.001), and TIMI major bleeding related to CABG (HR 4.73; 95% CI: 1.90 – 11.82; P <0.001).

Prespecified as well as post hoc subgroup analyses in TRITON-TIMI 38 trial identified subgroups of interest that had different clinical efficacy and absolute levels of bleeding than the overall cohort, resulting in less or greater net clinical benefit or clinical harm.[18] Accordingly, there was evidence of net harm with prasugrel in patients with a history of cerebrovascular events. In addition, there was no apparent net clinical benefit in patients >75 years of age and in patients with low body weight (<60 kg). Greater benefit without increased risk of bleeding was observed in diabetic patients. There was no difference in efficacy in patients with (CrCl <60 mL/min) or without (CrCl >60 mL/min) renal impairment. Although reduction in the rate of ischemic events by means of more than one antiplatelet agent has uniformly been accompanied by an increase in bleeding, a benefit with prasugrel with regard to the primary end-point was found both with the use of glycoprotein IIb/IIIa-receptor antagonists during the index hospitalization (HR for prasugrel vs. clopidogrel, 0.79; 95% CI: 0.69 – 0.91; P<0.001) or without such use (HR 0.84; 95% CI: 0.72 – 0.99; P = 0.03). Moreover, the beneficial effects of prasugrel with regard to ischemic outcomes and stent thrombosis, as compared to clopidogrel, were statistically robust irrespective of stent type,[19] and these data affirm the importance of intensive platelet inhibition in patients with intracoronary stents.

In the NSTE-ACS sub-cohort of the TRITON-TIMI 38 trial (10,074 patients), the composite primary efficacy end-point rate was also lower among patients receiving prasugrel (9.3% vs. 11.2%; HR 0.82; 95% CI: 0.73 – 0.93; P = 0.002), mostly driven by a significant risk reduction for MI (from 9.2% to 7.1%; RRR 23.9%; 95% CI: 12.7 – 33.7; P < 0.001), as it was in the whole cohort. There was no difference in the rates of either non-fatal stroke or cardiovascular death. Bleeding risks were along with those in the whole cohort of the TRITON-TIMI 38 trial.[18] Figures for stent thrombosis rate for NSTE-ACS patients, however, are not available.

In the STEMI sub-cohort of the TRITON-TIMI 38 trial (3,534 patients),[20] benefits of prasugrel therapy appeared very early. At 30 days, prasugrel therapy was associated with a significantly lower incidence of the composite primary efficacy end-point (6.5% vs. 9.5%; HR 0.68; 95% CI: 0.54 – 0.87; P = 0.0017; NNT 35), MI (4.9% vs. 7.0%; HR 0.70; 95% CI: 0.53 – 0.92; P = 0.0106; NNT 49), and stent thrombosis (2.4% 1.2%; HR 0.49; 95% CI: 0.28 – 0.84; P = 0.0084; NNT 81) without significant increase in the incidence of non-CABG-related TIMI major bleeding (1.3% vs. 1.0%; HR 0.74; 95% CI: 0.39 – 1.38; P = 0.3359). Also, there was no difference in the rates of either non-fatal stroke or cardiovascular death. All these beneficial effects persisted unchangeable for 15 months. This finding was consistent with that in the population with unstable angina or non-STEMI, with no interaction noted between presenting syndrome and benefits of prasugrel (p = 0.7686). With regards to the safety, treatment with either prasugrel or clopidogrel did not differ with respect to non-CABG-related TIMI major bleeding at 30 days (P = 0.3359) and at 15 months (P = 0.6451). TIMI life-threatening bleeding and TIMI major or minor bleeding were also similar with the two treatment regimens, and only TIMI major bleeding after CABG surgery was significantly increased with prasugrel (P = 0.0033).

A small retrospective observational substudy of the TRITON-TIMI 38 trial involved 346 patients who had received either study drug and subsequently underwent isolated CABG at some point during the 15-month trial.[21] In spite of an increased risk of bleeding, patients treated with prasugrel prior to isolated CABG were observed to have significantly lower mortality compared to patients who received clopidogrel prior to CABG while enrolled in the TRITON-TIMI 38 study. It is noteworthy that almost all patients were back on their study drug within a week of surgery. However, these results must be interpreted with caution because the analysis consisted of small numbers.

TRITON-TIMI 38 trial tested prasugrel vs. clopidogrel in intermediate-to-high-risk patients with ACS undergoing PCI and demonstrated a significant benefit of prasugrel in reducing ischemic events, but with an increased risk of bleeding. Given this favorable result in ACS patients undergoing stenting, TRIGGER-PCI trial[45] attempted to compare prasugrel and clopidogrel in lower risk patients, as those with stable coronary artery disease who had just undergone elective PCI. Although the study was based on platelet-reactivity testing to guide antiplatelet therapy in this otherwise low-risk PCI population, it was prematurely halted due to futility. The ongoing TRILOGY ACS trial,[46] inspired predominantly from (**a**) trials which

demonstrated that clopidogrel added to aspirin was superior to aspirin alone to reduce ischemic events in ACS patients treated medically[3,6,8] and (**b**) the TRITON-TIMI 38 trial which showed the superiority of prasugrel over clopidogrel,[18] compares prasugrel and clopidogrel in exclusively medically managed NSTE ACS patients and will provide important information regarding the optimal approach to oral antiplatelet therapy for this high-risk, understudied population.

Except for bleeding, the rate of other adverse effects in TRITON-TIMI 38 study was similar to that of prasugrel and clopidogrel. Thrombocytopenia occurred at the same frequency in each group (0.3%) while neutropenia was less common with prasugrel (<0.1% vs. 0.2%; P = 0.02).

CONCLUSION

Prasugrel provides faster, more profound and less variable inhibition of platelet function than clopidogrel. Prasugrel, in contrast to clopidogrel, results in predictable and consistent antiplatelet response. In ACS patients with scheduled PCI, prasugrel therapy is associated with significantly reduced rates of ischemic events, MI, and stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding, and no benefit with regard to overall mortality. However, in STEMI patients undergoing PCI, the beneficial effects of prasugrel on the prevention of ischemic events, MI, and stent thrombosis are not associated with apparent excess in bleeding. To date, the superiority of prasugrel over clopidogrel has been demonstrated only in the setting of ACS patients undergoing PCI with stent implantation.

TICAGRELOR

Ticagrelor belongs to a novel chemical class, cyclopentyltriazolopyrimidine, and is a reversible and direct-acting oral antagonist of the ADP receptor P2Y12 with a plasma half-life of ~12 h. The level of P2Y12 inhibition is determined by the plasma ticagrelor level and, to a lesser extent, an active metabolite. Like prasugrel, it provides faster, greater and more consistent P2Y12 inhibition than clopidogrel, but additionally it has a quicker offset of action so that recovery of platelet function is faster (functional recovery of circulating platelets within ~48 hours). Notably, its action begins in the portal circulation immediately after intestine absorption in contrast to clopidogrel and prasugrel of which the inhibitory action begins in the systemic circulation after an enzymatic biotransformation in the liver. Ticagrelor increases levels of drugs metabolized through CYP3A, such as simvastatin, whilst moderate CYP3A inhibitors such as diltiazem increase the levels and reduce the speed of offset of the effect of ticagrelor.[1,13,17,28]

PLATO, a randomized, double-blind trial, compared ticagrelor with clopidogrel for the prevention of vascular events in 18 624 ACS patients.[22] The study included patients with either moderate-to-high-risk NSTE-ACS (planned for either conservative or invasive management) or STEMI (planned for primary PCI). A substantial difference from the TRITON-TIMI 38 trial, which included only patients with ACSs treated exclusively with PCI, was the induction of patients with any ACS planned for invasive management and patients with NSTE-ACS planned only for medical management. Patients were randomly assigned to receive, in addition to aspirin, ticagrelor or clopidogrel. The treatment was continued for 6 to 15 months (median duration of study drug exposure of 9 months). The primary efficacy end-point was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke. The key safety end-point was major bleeding. In the overall cohort, ticagrelor therapy for 6 to 15 months was associated with a significantly lower rate of the primary composite efficacy end-point (9.8% vs. 11.7%; HR 0.84; 95% CI: 0.77 – 0.92; P <0.001), MI (5.8% vs. 6.9%; HR 0.84; 95% CI: 0.75 – 0.95; P = 0.005), definite stent thrombosis (1.3% vs. 1.9%; P <0.01), total mortality (4.5% vs. 5.9%; P < 0.001), and death from vascular causes (4.0% vs. 5.1%; HR 0.79; 95% CI: 0.69 – 0.91; P = 0.001). While reduction in stent thrombosis rates by ticagrelor were seen early, most of the benefit in terms of reduced MI and death occurred progressively over 12 months, with continued separation of event curves at 12 months. It is noteworthy that these benefits were observed mainly among patients with increased troponin levels. Indeed, those patients with a positive initial troponin had a significant reduction in the primary endpoint with ticagrelor compared with clopidogrel (10.3% vs. 12.3%, HR 0.85; 95% CI: 0.77 – 0.94) in contrast to patients with negative initial troponin (7.0% vs. 7.0%), as did those with a final diagnosis of NSTEMI (11.4% vs. 13.9%; HR 0.83; 95% CI: 0.73 – 0.94) compared with those with a final diagnosis of unstable angina (8.6% vs. 9.1% respectively; HR 0.96; 95% CI: 0.75 – 1.22). Regarding safety, treatment with ticagrelor and clopidogrel did not differ significantly with respect to rate of stroke (1.5% vs. 1.3%; P = 0.22) and overall PLATO-defined major bleeding (11.6% vs. 11.2%; P = 0.43) at the end of follow-up. However, though major bleeding related to CABG surgery was similar with the two treatments (7.4% vs. 7.9%; P = 0.32), non-CABG-related major bleeding was significantly increased with ticagrelor (4.5% vs. 3.8%; HR 1.19; 95% CI: 1.02 – 1.38; P = 0.03). Minor bleeding was likewise increased with ticagrelor compared with clopidogrel. There was no difference in the overall rates of fatal hemorrhage between the groups (0.3% in both groups). However, intracranial fatal hemorrhage was more frequent in the ticagrelor group (0.1% vs. 0.01%; P = 0.02) while non-intracranial fatal hemorrhage was more frequent in the clopidogrel group (0.1% vs. 0.3%; P = 0.03).

In the PLATO trial, 1261 patients underwent CABG while were on study drug treatment for <7 days before surgery.[23] As per protocol, ticagrelor or clopidogrel could be restarted when it was considered safe in terms of bleeding and be con-

tinued up to 12th month of study. In this subgroup of patients undergoing CABG within 7 days after the last study drug intake, ticagrelor compared with clopidogrel was associated with a substantial reduction in the primary composite efficacy end-point (10.6% vs. 13.1%; HR 0.84; 95% CI: 0.60 – 1.16; P = 0.29), total mortality (4.7% vs. 9.7%; HR 0.49; 95% CI: 0.32 – 0.77; P < 0.01), and cardiovascular mortality (4.1% vs. 7.9%; HR 0.52; 95% CI: 0.32 – 0.85; P < 0.01) without excess risk of CABG-related bleeding. Non-cardiovascular mortality was also numerically lower in the ticagrelor group (0.7% vs. 2.0%; P = 0.07). Interestingly, the above benefit with respect to the reduced mortality with ticagrelor appeared early within the first month and continued accruing progressively during the rest of the follow-up period. Thus, in post-ACS patients who will need CABG at any time during dual antiplatelet treatment, ticagrelor as compared with clopidogrel reduces early and late cardiovascular and total death following CABG without an increase in major bleeding. Given that the post-operative administration of clopidogrel in patients who undergo CABG within 180 days after MI has been associated with reduced total and cardiovascular mortality,[47] the above results are of great importance.

In patients with STEMI intended for reperfusion with primary PCI (N = 7,544), the effects of ticagrelor compared with clopidogrel were consistent with those seen in the overall PLATO trial.[24] Ticagrelor produced a consistent reduction in the primary composite efficacy end-point, cardiovascular and total death, MI, and stent thrombosis and improved survival without increasing major bleeding but with a higher rate of stroke. The absolute mortality reduction from ticagrelor over clopidogrel was of the same magnitude as that achieved with tissue plasminogen activator compared with streptokinase[48] but without the corresponding increase in intracranial bleeding and with a reduction in reinfarction not seen with thrombolysis. Furthermore, these benefits are obtained compared with active treatment with clopidogrel and on top of aspirin, primary PCI, and other evidence-based secondary prevention therapies widely used in PLATO patients.

In the context of PLATO trial, an early invasive strategy was planned at the time of randomization in 13,408 (72%) of 18,624 patients hospitalized for ACS, either STEMI (49.1%) or NSTE-ACS (50.9%).[25] PCI was carried out in 10,298 (76.8%) individuals, and CABG in 782 (5.8%) during first hospital admission. In this subgroup of patients intended for reperfusion with an early invasive strategy, patients given ticagrelor had significant reductions in primary and secondary composite efficacy end-point, cardiovascular and total deaths, MI, and stent thrombosis, without an increase in the risk of major bleeding or transfusion. The benefit of ticagrelor vs. clopidogrel for the composite primary efficacy end-point of cardiovascular death, myocardial infarction, or stroke was similar across a wide range of subgroups, irrespective of the loading dose of clopidogrel. In general, the benefits with respect to clinical events and stent thrombosis were consistent whether or not patients were given standard or higher loading doses of clopidogrel, as advocated for patients undergoing invasive strategies. However, the benefits of ticagrelor were most evident among patients with increased cardiac troponin, and the mortality benefit of ticagrelor was more notable in patients with non-STE-ACSs. It is estimated that the use of ticagrelor instead of clopidogrel for 1 year in 1000 patients with ACS and who are planned to undergo an invasive strategy at the start of drug treatment would lead to 11 fewer deaths, 13 fewer myocardial infarctions, and 6 fewer cases of stent thrombosis without an increase in the rates of major bleeding or transfusion. These results also support the idea that increased inhibition of platelet P2Y12 receptors in the setting of an invasive management of ACS can achieve substantial reduction in the rate of mortality when not associated with an increase in the rate of major bleeding. Thereby, ticagrelor has important advantages, and improves the early invasive and long-term management of patients with ACS.

Regarding the adverse effects, in addition to increased rates of minor or non-CABG-related major bleeding, therapy with ticagrelor may induce dyspnea, increased frequency of ventricular pauses, and asymptomatic increases in uric acid.[22,47,50] Dyspnea induced by ticagrelor occurs most frequently (up to 15%) within the first week of treatment and may be transient or persist until cessation of treatment, but only infrequently it is severe enough to cause discontinuation of treatment.[22,51] Dyspnea does not appear to be associated with any deterioration in cardiac or pulmonary function.[51] Ventricular pauses associated with ticagrelor mostly consist of asymptomatic nocturnal sinoatrial pauses; caution is advised in patients with either advanced sinoatrial disease or second- or third-degree atrioventricular block, unless already treated by permanent pacemaker. The mechanism for the dyspnea and ventricular pauses is uncertain. A slightly greater increase in serum creatinine was seen in the PLATO trial with ticagrelor compared with clopidogrel, but the difference was no longer apparent 1 month after cessation of treatment.[22] Rates of gastrointestinal disturbance and rash are similar with ticagrelor compared with clopidogrel.[50]

CONCLUSION

Ticagrelor compared with clopidogrel provides faster, more profound and less variable inhibition of platelet function and results in predictable and consistent antiplatelet response. The above characteristics represent a profile similar to that of prasugrel, but additionally ticagrelor has a quicker offset of action so that recovery of platelet function theoretically is faster, within 2 – 3 days instead of >7 days for prasugrel. However, current recommendations advise that, like clopidogrel, ticagrelor should also be stopped 5 days before surgery. In patients who have an ACS with or without ST-segment elevation, ticagrelor therapy compared to that of clopidogrel significantly reduces the rate of overall major ischemic events, cardiovas-

cular death, all-cause mortality, MI, and stent thrombosis and improves survival without increasing overall major bleeding but with a higher rate of non–procedure-related bleeding, including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types. The benefit of ticagrelor vs. clopidogrel with respect to reduction of major cardiovascular events is similar across a wide range of subgroups regardless of the loading dose of clopidogrel and regardless of whether invasive or noninvasive management is planned. In addition, the survival benefit from more-intense platelet inhibition with ticagrelor in patients with ACS is consistent with reductions in the mortality rate obtained by means of platelet inhibition with aspirin in patients with ACS[52,53] and with clopidogrel in patients with STEMI.[54] It is noteworthy that all these benefits are observed mainly among patients with increased troponin levels. Furthermore, the beneficial effect of ticagrelor compared to that of clopidogrel is seen early and continues accruing progressively over time, with continued separation of event curves at 12 months. This duration of treatment benefit has also been shown with clopidogrel.[55] Thus, ticagrelor appears to expand on the previously demonstrated benefits of clopidogrel across the spectrum of ACS. Moreover, the incremental reduction in the risk of coronary thrombotic events in ACS patients undergoing PCI through more-intense P2Y12 inhibition with ticagrelor is consistent with similar effects of prasugrel.[18] However, the most impressive distinction of ticagrelor from the other two oral potent inhibitors of P2Y12 receptors is a robust reduction of the rate of death that appears early and then continues increasing over time, effects not seen with clopidogrel or prasugrel. This advantage of ticagrelor over clopidogrel in terms of reduced mortality is similar in magnitude to other major advances, such as streptokinase or aspirin vs. placebo,[56] tissue plasminogen activator vs. streptokinase,[48] and primary PCI vs. tissue plasminogen activator,[57] in care of patients with STEMI. However, the mortality benefit with ticagrelor is more notable in patients with non-STE-ACS treated with PCI, particularly those with an increase in cardiac troponin, when previous antithrombotic treatments were unsuccessful in improving survival by a reduction in ischemic events.[2,18,53,58-61] These findings show that, compared with the benefits noted with clopidogrel vs. placebo, additional protection from ischemic events can be achieved with ticagrelor.

CANGRELOR

Withholding P2Y12 inhibitors because of the risk for bleeding in the case of a necessary or mandatory non-coronary cardiac or non-cardiac surgical procedure or in the case of an imminent CABG surgery may lead to an increased rate of thrombotic events. Interruption of DAPT soon after stent implantation or after initiation of DAPT for the management of ACS, specifically in high risk cohorts such as those with ongoing ischemia in presence of high risk coronary anatomy, increases excessively the risk of coronary thrombotic complications, which carries a particularly adverse prognosis.[30-37] As the overall periprocedural time window of withdrawal of a P2Y12 inhibitor is major determinant of the consequent coronary thrombosis as well as the ensuing bleeding,[26,35] the advent of a P2Y12 receptor inhibitor characterized by rapid, potent, predictable, and reversible platelet inhibition with very rapid offset of effect might be of great value for patients in whom discontinuation of antiplatelet therapy, particularly a P2Y12 receptor inhibitor, can lead to adverse consequences while preserving normal hemostasis at the time of surgery.[1,2,39,62]

Cangrelor, a nonthienopyridine adenosine triphosphate analogue, is an IV administered direct-acting, selective, and specific P2Y12 inhibitor. It is characterized by rapid, potent, predictable, and reversible platelet inhibition with very rapid offset of its effect.[13,38,63] In particular, cangrelor is metabolized through dephosphorylation pathways and has a plasma half-life of 3 to 6 minutes. When given as a bolus plus infusion, quickly and consistently inhibits platelets to a high degree, with normalization of platelet function within 30 to 60 minutes after discontinuation.[63] Moreover, cangrelor has an additional antiplatelet effect when added in vitro to the platelets of patients receiving long-term treatment with clopidogrel.[64,65] A phase 2 trial involving patients undergoing PCI showed dose-dependent platelet inhibition similar to that of abciximab (a IIB/IIIa antagonist), less prolongation of bleeding time, and a more rapid return to platelet function.[66] Therefore, this compound might have a role in the treatment of patients who require rapid, predictable, and profound but very fast reverse of platelet inhibition.

Cangrelor has been studied in two large, phase 3, randomized clinical trials. Interestingly, both studies were stopped when an interim analysis concluded that the trials would be unlikely to show superiority for the primary end point. CHAMPION PLATFORM trial[67] examined the efficacy of cangrelor vs. placebo administered to NSTE-ACS patients during PCI, with patients in the placebo group subsequently receiving a loading dose of 600 mg of clopidogrel at the end of the revascularization procedure and patients in the cangrelor group receiving 600 mg of clopidogrel at the end of the infusion, at least 2 hours after PCI. The primary efficacy end point was a composite of death from any cause, MI, or ischemia-driven revascularization at 48 hours. In this trial, the use of periprocedural cangrelor during PCI was not superior to placebo in reducing the composite primary end point. However, in the cangrelor group, as compared with the placebo group, two prespecified secondary end points were significantly reduced at 48 hours. Indeed, the rate of stent thrombosis was significantly lower in the cangrelor group (0.2% vs. 0.6%; odds ratio-OR 0.31; 95% CI: 0.11 – 0.85; P = 0.02) and the difference was still significant at 30 days. Likewise, the rate of death from any cause was significantly lower in the cangrelor group (0.2%

vs. 0.7%; OR 0.33; 95% CI: 0.13 – 0.83; P = 0.02), though at 30 days, this difference was no longer significant. Given the rapid effect on platelet inhibition seen in the CHAMPION platelet substudy, these reductions in stent thrombosis and death are biologically plausible. With regards to safety, there was no significant difference in the rate of blood transfusion (P = 0.13), though major bleeding on one scale was increased in the cangrelor group (5.5% vs. 3.5%; P<0.001) because of more groin hematomas.

CHAMPION PCI trial[68] compared IV cangrelor with 600 mg of oral clopidogrel administered before PCI in patients with ACS. Cangrelor was administered IV 30 minutes before PCI and continued for at least 2 hours after PCI, with patients in the cangrelor group subsequently receiving a loading dose of 600 mg of clopidogrel at the end of the infusion. An oral loading dose of 600 mg of clopidogrel was given 30 minutes before PCI in the patients of the clopidogrel group. The primary efficacy end point was a composite of death from any cause, MI, or ischemia-driven revascularization at 48 hours. In this trial, IV cangrelor was not superior to a 600-mg loading dose of clopidogrel, administered 30 minutes before PCI, in reducing the composite primary efficacy end point (7.5% vs. 7.1%; OR 1.05; 95% CI: 0.88 – 1.24; P = 0.59). Likewise, cangrelor was not superior at 30 days. Minor bleeding was more common in patients who received cangrelor, and one measure of major bleeding (based on criteria from the ACUITY trial[69]) showed a trend toward an increase in bleeding with cangrelor as compared with clopidogrel. In addition, a secondary exploratory end point of death from any cause, Q-wave MI, or ischemia-driven revascularization showed a trend toward a reduction with cangrelor, but it was not significant (0.6% vs. 0.9%; OR 0.67; 95% CI: 0.39 – 1.14; P = 0.14).

The BRIDGE trial[40] evaluated the hypothesis that cangrelor may be a safe and effective drug to bridge patients from irreversible platelet P2Y12 inhibitors to open heart surgery. The trial involved 210 patients with an ACS or treated with a coronary stent and receiving a thienopyridine, awaiting CABG surgery. Thienopyridines were stopped and patients were administered cangrelor or placebo for the thienopyridine-free time frame (for at least 48 hours). Study drug was discontinued 1 to 6 hours before CABG surgery and was not administered during or after CABG surgery. The primary efficacy end point was platelet reactivity (measured in P2Y12 reaction units [PRUs]), assessed daily. Specifically, the aim was to assess whether a cangrelor IV infusion would maintain levels of platelet reactivity of less than 240 PRUs throughout the preoperative period as measured by the VerifyNow P2Y12 assay. Of note, such a level of platelet reactivity is known to be associated with a low risk of thrombotic events. This level approximated the levels of platelet reactivity expected to be maintained if a thienopyridine had not been discontinued.[70,71] The main safety end point was excessive CABG surgery-related bleeding. In this trial, it was shown that the proportion of patients with low levels of platelet reactivity throughout the entire treatment period was significantly greater in the cagrelor group than in the placebo group (98.8% vs. 19.0%; RR 5.2 [95% C: 3.3 – 8.1]; P < 0.001). The rates of excessive CABG-related bleeding were similar between the two groups (11.8% vs. 10.4%; RR 1.1 [95% CI: 0.5 – 2.5] P = 0.763). In addition, bridging with a prolonged infusion of cangrelor did not increase major bleeding prior to CABG surgery, although minor bleeding episodes were numerically higher with cangrelor. Thus, in this trial, cangrelor achieved and maintained target levels of platelet inhibition known to be associated with a low risk of thrombotic events compared with placebo, without a significant excess in bleeding complications. The trial was not planned and not powered to show differences in ischemic events. Of note, this hypothesis had previously been tested in the CHAMPION PCI trial.[68] This trial showed that treatments with cagrelor and clopidogrel did not differ with respect to the primary end-point of death from any cause, MI, or ischemia-driven revascularization at 48 hours.[68]

CONCLUSION

Cangrelor, a nonthienopyridine ATP analogue, is an IV administered direct-acting, selective, and specific P2Y12 receptor inhibitor characterized by rapid, potent, predictable, and reversible platelet inhibition with very rapid offset of its effect. However, the most important clinically relevant characteristic of cagrelor is the very fast offset of its antiplatelet effect, with normalization of platelet function within 30 to 60 minutes after discontinuation. Therefore, this compound might have a role in the treatment of patients who require rapid, predictable, and profound but very fast reverse of platelet inhibition. Indeed, among patients who discontinue thienopyridine therapy prior to cardiac surgery, the prolonged infusion of cangrelor throughout the thienopyridine-free time frame maintains an effective therapeutic level of platelet inhibition without an increase in major bleeding prior to CABG or excessive CABG-related bleeding.[40] Regarding the efficacy of cangrelor administered to NSTE-ACS patients during PCI, the CHAMPION PLATFORM trial failed to show any benefit in terms of reducing death, MI, or ischemia-driven revascularization at 48 hours. Despite this negative result, however, the rates of stent thrombosis and death were reduced very early, within the first 48 hours, with no significant increase in bleeding, except for groin hematomas.[67] Given the rapid effect on platelet inhibition seen in the CHAMPION platelet substudy, these reductions in stent thrombosis and death are biologically plausible, and might be of value in the clinical setting. With regards to the comparison of cangrelor with clopidogrel in the setting of patients with ACS undergoing PCI, it has been shown that periprocedural IV cangrelor was not superior to a 600-mg loading dose of clopidogrel, administered 30 minutes before PCI, in reducing the composite end point of death from any cause, myocardial infarction, or ischemia-driven revascu-

larization at 48 hours.[68] To date, the most meaningful result from the clinical trials of cangrelor is that IV cangrelor is a feasible management strategy in patients waiting for cardiac surgery who require prolonged platelet P2Y12 inhibition after thienopyridine discontinuation.

REFERENCES

1. Patrono C, Andreotti F, Arnesen H, et al. Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011; 32:2922-2932.
2. Eikelboom JW, Hirsh J, Spencer FA, et al. Antiplatelet Drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(suppl 2):e89S-e119S.
3. CURE investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *NEJM* 2001; 345:494–502. [Errata, *N Engl J Med* 2001; 345:1506, 1716.].
4. Mehta S, Yusuf S, Peters R, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; 358:527–533.
5. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; 288:2411-2420. [Erratum, *JAMA* 2003; 289:987.]
6. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352:1179-1189.
7. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolysis (The PCI-CLARITY study). *JAMA* 2005; 294:1224-1232A.
8. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 2005; 366:1607-21
9. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol* 2007; 49:1505–1516.
10. Wallentin L. P2Y12 inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J* 2009; 30:1964–1977.
11. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009; 360:363-375.
12. Schφmig A. Ticagrelor – Is there need for a new player in the antiplatelet-therapy field? *N Engl J Med* 2009; 361:1108-1111.
13. Cattaneo M. New P2Y12 inhibitors. *Circulation* 2010; 121:171–179.
14. Mega JL, Close SL, Wiviott SD, et al. Genetic variants in ABCB1 and CYP2C19 and cardiovascular outcomes after treatment with clopidogrel and prasugrel in the TRITON-TIMI 38 trial: a pharmacogenetic analysis. *Lancet* 2010; 376:1312–1319.
15. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 2010; 304:1821–1830.
16. Kuliczkowski W, Witkowski A, Polonski L, et al. Interindividual variability in the response to oral antiplatelet drugs: a position paper of the Working Group on antiplatelet drugs resistance appointed by the Section of Cardiovascular Interventions of the Polish Cardiac Society, endorsed by the Working Group on Thrombosis of the European Society of Cardiology. *Eur Heart J* 2009; 30:426-435.
17. Tantry US, Bliden KP, Wei C, et al. First analysis of the relation between CYP2C19 genotype and pharmacodynamics in patients treated with ticagrelor versus clopidogrel: The ONSET/OFFSET and RESPOND genotype studies. *Circ Cardiovasc Genet* 2010; 3:556-566.
18. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357:2001-2015.
19. Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischaemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomised trial. *Lancet* 2008; 371:1353-1363.
20. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009; 373:723-731.
21. Small TRITON substudy hints at better survival with prasugrel in CABG patients. November 18, 2010, http://www.theheart.org/article/1154085/print.do
22. Lars Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med* 2009; 361:1045-1057.
23. Held C, Esenblad N, Bassand JP, et al. Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery: Results From the PLATO (Platelet Inhibition and Patient Outcomes) Trial. *J Am Coll Cardiol* 2011; 57:672-684.
24. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation* 2010; 122:2131-2141.
25. Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet* 2010; 375:283-293.
26. Wijns W, Kolh P, Danchin N, et al; Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Sur-

gery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI). Guidelines on myocardial revascularization. *Eur Heart J* 2010; 31:2501-2555.
27. Anderson JL, Adams CD, Antman EM, et al. 2011 WRITING GROUP MEMBERS, ACCF/AHA TASK FORCE MEMBERS. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/Non-ST-elevation myocardial infarction: a report of the ACCF/AHA Task Force on Practice Guidelines. *Circulation* 2011; 123:e426-e579.
28. Hamm CW, Bassand JP, Agewall S, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011; 32(23):2999-3054.
29. Levine GN, Bates ER, Blankenship JC, et al. 2011 WRITING GROUP MEMBERS, ACCF/AHA TASK FORCE MEMBERS. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011; 58:e44-e122.
30. Ho PM, Peterson ED, Wang L, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008; 299(5):532-539.
31. Boggon R, van Staa TP, Timmis A, et al. Clopidogrel discontinuation after acute coronary syndromes: frequency, predictors and associations with death and myocardial infarction – a hospital registry-primary care linked cohort (MINAP-GPRD). *Eur Heart J* 2011; 32(19):2376-2386.
32. Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. *Circulation* 2004; 110(16):2361-2367.
33. Ho PM, Tsai TT, Wang TY, et al. Adverse events after stopping clopidogrel in post-acute coronary syndrome patients: insights from a large integrated healthcare delivery system. *Circ Cardiovasc Qual Outcomes* 2010; 3(3):303-308.
34. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting vs. bare-metal stents. *J Am Coll Cardiol* 2006; 48(12):2584-2591.
35. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; 293(17):2126-2130.
36. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006; 113(24):2803-2809.
37. Rossini R, Capodanno D, Lettieri C, et al. Prevalence, predictors, and long-term prognosis of premature discontinuation of oral antiplatelet therapy after drug eluting stent implantation. *Am J Cardiol* 2011; 107:186-194.
38. Ferreiro JL, Ueno M, Angiolillo DJ. Cangrelor: a review on its mechanism of action and clinical development. *Expert Rev Cardiovasc Ther* 2009; 7(10):1195-1201.
39. Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. *J Am Coll Cardiol* 2007; 49:2145-2150.
40. Angiolillo DJ, Firstenberg MS, Price MJ, et al. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: A randomized controlled trial. *JAMA* 2012; 307:265-274.
41. Jakubowski JA, Winters KJ, Naganuma H, et al: a novel thienopyridine antiplatelet agent. A review of preclinical and clinical studies and the mechanistic basis for its distinct antiplatelet profile. *Cardiovasc Drug Rev* 2007; 25:357-374.
42. Erlinge D, Varenhorst C, Braun OÖ, James S, et al. Patients with poor responsiveness to thienopyridine treatment or with diabetes have lower levels of circulating active metabolite, but their platelets respond normally to active metabolite added ex vivo. *J Am Coll Cardiol* 2008; 52:1968–1977.
43. Michelson AD, Frelinger AL III, Braunwald E, et al; for the TRITON-TIMI 38 Investigators. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. *Eur Heart J* 2009; 30:1753–1763.
44. Farid NA, Kurihara A, Wrighton S. Metabolism and disposition of the thienopyridine antiplatelet drugs ticlopidine, clopidogrel, and prasugrel in humans. *J Clin Pharmacol* 2010;50:126–142.
45. Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel (TRIGGER-PCI) trial. November 10, 2011, http://www.theheart.org/article/1307693/print.do
46. Chin CT, Roe MT, Fox KA, et al. Study design and rationale of a comparison of prasugrel and clopidogrel in medically managed patients with unstable angina/non–ST-segment elevation myocardial infarction: The TaRgeted platelet Inhibition to cLarify the Optimal strateGy to medically manage Acute Coronary Syndromes (TRILOGY ACS) trial. *Am Heart J* 2010; 160:16-22.
47. Sørensen R, Abildstrøm SZ, Hansen PR, et al. Efficacy of Post-Operative Clopidogrel Treatment in Patients Revascularized With Coronary Artery Bypass Grafting After Myocardial Infarction. *J Am Coll Cardiol* 2011; 57:1202–1209.
48. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction: the GUSTO Investigators. *N Engl J Med* 1993; 329:673-682.
49. Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* 2006; 27:1038-1047.
50. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the First reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 Trial. *J Am Coll*

Cardiol 2007; 50:1844-1851.
51. Storey RF, Bliden K, Patil SB, et al. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel or placebo in the ONSET/OFFSET Study. *J Am Coll Cardiol* 2010; 56:185-193.
52. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; 2:349-360.
53. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324:71-86.
54. Bonello L, Camoin-Jau L, Armero S, et al. Tailored clopidogrel loading dose according to platelet reactivity monitoring to prevent acute and subacute stent thrombosis. *Am J Cardiol* 2009; 103:5-10.
55. Yusuf S, Mehta SR, Zhao F, et al. Early and late effects of clopidogrel in patients with acute coronary syndromes. *Circulation* 2003; 107:966-972.
56. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2: 349–360.
57. Boersma E. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J* 2006; 27:779-788.
58. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345:494-502.
59. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. *Lancet* 2002; 359:189-198.
60. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000; 355:1936-1942.
61. Mehta SR, Cannon CP, Fox KA, et al. Routine vs. selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005; 293:2908-2917.
62. Douketis JD, Spyropoulos AC, A. Spencer FA, et al. Perioperative Management of Antithrombotic Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141(suppl 2):e326S-e350S.
63. Storey RF, Sanderson HM, White AE, et al. The central role of the P(2T) receptor in amplification of human platelet activation, aggregation, secretion and procoagulant activity. *Br J Haematol* 2000; 110:925-934.
64. Storey RF, Wilcox RG, Heptinstall S. Comparison of the pharmacodynamic effects of the platelet ADP receptor antagonists clopidogrel and AR-C69931MX in patients with ischaemic heart disease. *Platelets* 2002; 13:407-413.
65. Behan MW, Fox SC, Heptinstall S, Storey RF. Inhibitory effects of P2Y12 receptor antagonists on TRAP-induced platelet aggregation, procoagulant activity, microparticle formation and intracellular calcium responses in patients with acute coronary syndromes. *Platelets* 2005; 16:73-80.
66. Greenbaum AB, Grines CL, Bittl JA, et al. Initial experience with an intravenous P2Y12 platelet receptor antagonist in patients undergoing percutaneous coronary intervention: results from a 2-part, phase II, multicenter, randomized, placebo- and active-controlled trial. *Am Heart J* 2006; 151(3):689.e1-689.e10.
67. Bhatt DL, Lincoff AM, Gibson CM, et al. Intravenous Platelet Blockade with Cangrelor during PCI. *N Engl J Med* 2009; 361:2330-2341.
68. Harrington RA, Stone GW, McNulty S, et al. Platelet Inhibition with Cangrelor in Patients Undergoing PCI. *N Engl J Med* 2009; 361:2318-2329.
69. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355:2203-2216.
70. Price MJ. Bedside evaluation of thienopyridine antiplatelet therapy. *Circulation* 2009; 119:2625-2632.
71. Malinin A, Pokov A, Spergling M, et al. Monitoring platelet inhibition after clopidogrel with the VerifyNow-P2Y12(R) rapid analyzer: the VERIfy Thrombosis risk ASsessment (VERITAS) study. *Thromb Res* 2007; 119(3):277-284.